Cross-Discipline Team Leader Review

Date	September 16, 2025
From	Philip H. Sheridan, MD Emily Freilich, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 218879 Class 2 Resubmission
Applicant	OWP Pharmaceuticals, Inc.
Date of Submission	March 17, 2025
PDUFA Goal Date	September 17, 2025
Proprietary Name	Subvenite
Established or Proper Name	Lamotrigine Oral Suspension
Dosage Form(s)	Oral Suspension 10 mg/ml
Applicant Proposed Indication/Population	Epilepsy: Subvenite is indicated as adjunctive therapy for the following seizure types in patients aged 2 years and older: • partial-onset seizures. • primary generalized tonic-clonic (PGTC) seizures. • generalized seizures of Lennox-Gastaut syndrome. Subvenite is indicated for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED). Bipolar Disorder: Subvenite is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of

	mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.
Applicant Proposed Dosing Regimen	Dosing is the same as for the listed drug, Lamictal. The numerous dosing tables in the Lamictal prescribing information are based on concomitant medications, indication, and patient age and are proposed for the Subvenite prescribing information.
Recommendation on Regulatory Action	Approval

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Subvenite (lamotrigine oral suspension, 10 mg/ml) is a new formulation of an already approved drug (lamotrigine). Subvenite is proposed for the same indications as the listed drug (LD), Lamictal (lamotrigine) tablets, NDA 020241:

1. as adjunctive therapy for the following seizure types in patients aged 2 years and older:
   - partial-onset seizures.
   - primary generalized tonic-clonic (PGTC) seizures.
   - generalized seizures of Lennox-Gastaut syndrome.
2. for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).
3. for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

This submission is a Class 2 NDA resubmission of this 505(b)(2) application using Lamictal (lamotrigine) tablets, approved under NDA 020241, as the LD. The determination of benefit and risk for this new formulation of lamotrigine depends on the previous findings of effectiveness and safety for the LD and on a demonstration of adequate bridging with bioavailability and bioequivalence studies from Subvenite to the LD.

Lamotrigine is currently marketed as immediate release tablets, extended-release tablets, orally disintegrating tablets, and tablets for suspension.

Lamotrigine has a well characterized safety profile. The primary risk associated with lamotrigine use is that of severe allergic reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and multiorgan hypersensitivity reactions (drug reaction with eosinophilia and systemic symptoms, DRESS). Additional risks include hemophagocytic lymphohistiocytosis, cardiac rhythm and conduction abnormalities, blood dyscrasias, aseptic meningitis, suicidal behavior and ideation, and medication errors. Common adverse reactions with lamotrigine use include dizziness, headache, diplopia, ataxia, nausea, vomiting, abdominal pain, blurred vision, and somnolence. Despite these risks and adverse reactions, lamotrigine has proven to be an effective medication for the treatment of epilepsy and bipolar disorder.

Subvenite has been shown to have comparative bioavailability to the LD, Lamictal, in a pivotal comparative bioavailability study and a food effect study in healthy adult volunteers. No new or unexpected adverse events were discovered in the course of the development program of Subvenite in healthy adult volunteers.

When this NDA was previously submitted on March 4, 2024, the Office of Product Quality (OPQ) review team found that the Applicant had failed to adequately characterize the identity, strength, and purity of the proposed drug product); therefore, the NDA received a Complete Response on January 3, 2025. In this current Class 2 resubmission, the Applicant has successfully addressed the previous OPQ-identified deficiences.in the NDA.

A more detailed benefit risk assessment is presented in the Cross-Discipline Team Leader (CDTL) summary review, dated January 3, 2025, of the original NDA submission.

2. Background

This 505(b)(2) Class 2 NDA resubmission for Subvenite (lamotrigine) relies on the Agency's findings of safety and effectiveness for the LD, Lamictal 100 mg tablet (NDA 020241), which was approved in 1994.

In the original NDA submission of March 4, 2024, the Applicant provided evidence from two Phase 1 clinical pharmacology studies that Subvenite has similar bioavailability to that of the LD. However, due to Product Quality deficiencies, this application received a Complete Response letter on January 3, 2025.

Key Regulatory History since January 2025

Significant interactions between FDA and the Applicant include the following:

March 17, 2025	Class 2 Resubmission of NSA 218879
August 12, 2025	Pediatric Research Committee (PeRC) concurred with the Division's plan to issue two PREA PMRs to address the use of Subvenite in pediatric patients 1 month to less than 2 years of age for the epilepsy indications

August 15, 2025 Agreement with Applicant on Postmarketing Requirements and milestone dates

September 15, 2025 Agreement with Applicant on prescribing information and medication guide.

3. Product Quality

The technical lead for the Office of Product Quality (OPQ) review team was Dr. Martha Heimann, and the reviewers were Dr. Grace Chiou, Dr. Martha Heimann, and Dr. Julia Pinto (drug product/labeling); Dr. Khalid Khan and Dr. Tianhong Tim Zhou (manufacturing); Dr. Swapna Parnu and Dr. Ta-Chen Wu (biopharmaceutics); and Erica Keafer (regulatory business process manager).

During the previous review of the original NDA submission, the OPQ review team had determined that the proposed drug substance, microbiology, and labeling were adequate. However, the OPQ review team had found that the Applicant had not provided adequate information on the proposed drug product to ensure its identity, strength, and purity. The outstanding deficiencies of the original application were related to inadequate information to support acceptable quality control of the drug product. The reviewers noted in their review of the original NDA that "extensive deficiencies related to the proposed dissolution method, validation of analytical methods used for release and stability testing, lack of in-use stability data, and control of container closure leachables were communicated as information requests (IRs) early in the review cycle. The Applicant adequately addressed some of the IRs; however, the responses to the remaining IRs are either incomplete (i.e., 'reports to be submitted at a later time') or inadequate."

In addition, during the review of the original NDA submission, the OPQ team was advised by the Office of Regulatory Affairs that the manufacturing inspection made a (b) (4) recommendation for one of the drug substance manufacturing facilities (b) (4) .

Therefore, although the other discipline reviews recommended approval, the OPQ review team recommended a Complete Response to the original NDA submission due to these deficiencies as summarized in the Complete Response letter of January 3, 2025.

After review of the current NDA resubmission, the OPQ reviewers now state, "The applicant has provided adequate information to ensure the identity, strength, quality, and purity and performance for this drug/device combination product. The overall manufacturing

inspection recommendation is approved for all facilities associated with this application. The proposed labeling is acceptable from a product quality perspective . . .The applicant has withdrawn both (b) (4) sites. All remaining facilities are acceptable." (Executive Summery, OPQ NDA 218879 Integrated Quality Assessment, August 19, 2025, pages 2-3)

The OPQ review team therefore recommends Approval of NDA 218879 Subvenite.

4. Nonclinical Pharmacology/Toxicology

No nonclinical data were submitted in this application, and no nonclinical issues arose during review of this application. Therefore, a nonclinical pharmacology/toxicology review was not conducted.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted in this application, and no new clinical pharmacology issues arose during review of this application. Therefore, a new review by the Office of Clinical Pharmacology (OCP) was not conducted.

The OCP review team review of the original NDA application, dated December 18, 2024, was written by Dr. Dawei Li (primary reviewer) and Dr. Yun Xu (secondary reviewer). The two key clinical pharmacology studies were noted to be a pivotal bioavailability and bioequivalence (BA/BE) study under fasting conditions (Study LAMO-159-22) and a food effect study (Study LAMO-160-22). Based on these studies, the OCP review team concluded that the Applicant had provided adequate evidence that Subvenite has similar bioavailability to the LD, Lamictal, which constitutes an adequate scientific bridge. Therefore, the OCP review team recommended approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy data were submitted since the application relies on the previous finding of effectiveness for the LD and on the determination of the comparative bioavailability of Subvenite to the LD.

8. Safety

No new safety data were submitted in this application, and no new safety issues arose during review of this application. Therefore, no new safety review by the clinical safety reviewer, Dr. Amy Kao, was conducted.

Dr. Kevan VanLandingham, previous clinical safety reviewer, wrote the clinical safety review (dated January 2, 2025) of the original NDA submission. He concluded that no substantial new safety signal has been identified for Subvenite compared to the LD relied upon for a safety determination.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application.

10. Pediatrics

The Applicant had not submitted an Agreed initial Pediatric Study Plan (iPSP) prior to the original submission of this NDA. Therefore, the Division presented a plan to the Pediatric Research Committee (PeRC) that, if the NDA were to be approved, a postmarketing requirement (PMR) (rather than the iPSP) would address the PREA requirement to study this formulation for the treatment of partial onset seizures in pediatric patients 1 month to less than 2 years of age. The Division of Psychiatry had determined that no further studies are required for the pediatric indication of bipolar disorder because of an earlier negative study in pediatric patients 10 to 17 years of age. The PeRC agreed with this plan on November 19, 2024.

The planned PMRs were communicated to the Applicant in the 8-week Postmarketing Requirement Communication letter dated November 7, 2024. After the Class 2 resubmission of the NDA, the PeRC again reviewed the proposed PMRs on August 12, 2025, and concurred with the Division's plan. See Section 13 of this CDTL Summary Review for the PMRs as stated in the approval letter.

11. Other Relevant Regulatory Issues

Dr. VanLandingham determined that there were no investigators with disclosable financial interests/arrangements in the two clinical pharmacology studies submitted with the original NDA application.

The Division of Medication Error Prevention and Analysis 2 (DMEPA2) review (based on its evaluation of the proposed Prescribing Information, medication guide, and container label and carton labeling) provided specific recommendations to include in negotiations with the Applicant.

The Division of Medical Policy Programs (DMPP) review of the proposed Medication Guide provided specific recommendations to include in the labeling negotiations with the Applicant.

12. Labeling

Refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed, and the Applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

There is no need for a Risk Evaluation and Management Strategy (REMS) for this drug product because the LD used to establish safety for Subvenite in the context of this 505(b)(2) submission does not have a REMS, and the additional data submitted for Subvenite in the original NDA submission did not identify any new safety signals.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

See Section 10 (Pediatrics) of this CDTL summary review for the history of the required PMR studies.

The required PMR studies, as stated in the NDA approval letter, are as follows:

4884-1 Conduct a study to evaluate the pharmacokinetics, safety, and tolerability of an age-appropriate formulation of lamotrigine oral suspension (Subvenite) to determine a dosing regimen for partial-onset seizures in pediatric patients 1 month to less than 2 years of age. The study should identify the drug exposure that is similar to the exposure that is effective in patients 2 years and older with partial-onset seizures.

Draft Protocol Submission:	03/2026
Final Protocol Submission:	07/2026
Study Completion:	07/2028
Final Report Submission:	01/2029

4884-2 Conduct a long-term open-label safety study of lamotrigine oral suspension (Subvenite) in pediatric patients 1 month to 2 years of age.

Draft Protocol Submission:	03/2026
Final Protocol Submission:	01/2029
Study Completion:	01/2031
Final Report Submission:	07/2031

There are no planned postmarketing commitments for this NDA.

14. Recommended Comments to the Applicant

See the Approval letter.

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/s/

PHILIP H SHERIDAN
09/16/2025 09:09:08 AM

EMILY R FREILICH
09/16/2025 09:26:26 AM
On behalf of DN2